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REMARKS

Status of the Claims

Claims 1-28, 32-39, 42-48, 52, 54-64, 69 and 72-101 are pending herein.

Claims 4, 7, 11, 14, 19-22, 24, 25, 32, 33, 43, 56-60, 62-64, 72-75, 80-85 and 87-89 have been withdrawn.

Support for the amendment to claim 1 can be found, for instance, in original claim 31.

Support for the amendment to claim 52 can be found, for instance, in paragraph [0101] of the original specification.

Support for new claims 90 and 92 can be found, for example, in original claims 2, 6, 10 and 12.

Support for new claims 91 and 93 can be found, for example, in original claim 28 and paragraph [0007] of the original specification.

Support for new claims 94 and 95 can be found, for example, in original claim 54.

Support for new claims 96, 97, 100 and 101 can be found, for example, in original claims 29 and 30.

Support for new claims 98 and 99 can be found, for example, in Example 1 and in paragraph [0101] of the original specification.

No new matter is added.

Double Patenting

Various pending claims have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 15-19, 24-26 and 35 of O'Hagan et al. US 6,884,435 (O'Hagan). This rejection and its supporting remarks are respectfully traversed.

For example, claim 1 of the present application is directed to microparticles comprising: (a) a biodegradable polymer; (b) a cationic surfactant; and (c) a first polynucleotide-containing species adsorbed on the surface of the microparticles, *wherein the adsorbed first polynucleotide-containing species constitutes at least 5 percent of the total weight of the microparticles, wherein*

the cationic surfactant is present during formation of the microparticles, and wherein no cationic surfactant removal step is conducted subsequent to formation of the microparticles.

This claim, for example, the italicized portion thereof, is neither taught nor suggested by the claims of US 6,884,435.

MPEP 804 notes that, when considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the *claim* of a patent, the patent specification can be used as a dictionary *to learn the meaning of a term* in the patent claim. However, the disclosure of the patent may not be used as prior art for purposes of an obviousness-type double patenting rejection.

The Examiner has responded, alleging that the patent specification was only used to "define" the term "microparticles" and not as prior art. The Examiner further urges that O'Hagan "defines" microparticles as having a macromolecule to microparticle ratio in the range of 0.1 to 0.5% and comprising 0.5 to 1% cationic detergent surfactant, thereby meeting the italicized limitations of claim 1 above. Applicant respectfully disagrees.

Instead of defining the term "microparticles" as alleged by the Examiner, O'Hagan actually defines the term "microparticle" as being "a particle of about 100 nm to about 150 μm in diameter, more preferably about 200 nm to about 30 μm in diameter, and most preferably about 500 nm to about 10 μm in diameter." See the "Definitions" section at col. 5, lines 1-10. Nothing in O'Hagan's definition of "microparticle" pertains to the amounts of macromolecule and detergent that must be present in a particle in order for it to be termed a "microparticle," much less the amounts of *polynucleotide-containing* macromolecules and *cationic* detergent required in claim 1.

Rather than using the disclosure of O'Hagan to learn the meaning of a term in the claims, the Examiner has instead used the disclosure of O'Hagan to provide missing claim limitations (i.e., the Examiner is using O'Hagan as if it were prior art), which is impermissible in conjunction with an obviousness-type double patenting rejection.

All other claims depend, directly or indirectly, from claim 1.

Moreover, even assuming solely for the sake of argument that the specification were to be fully available for use in an obviousness-type double patenting rejection (it is not), the present claims would still be patentable over O'Hagan for the reasons set forth below.

Reconsideration and withdrawal of the outstanding nonstatutory obviousness-type double patenting rejection are requested.

Provisional Double Patenting

Various claims have been provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over certain claims of copending Application No. 11/113,861. This rejection is a *provisional* rejection. As noted in MPEP 804 I B (emphasis added):

> Occasionally, the Examiner becomes aware of two copending applications...that would raise an issue of double patenting ***if one of the applications became a patent.*** ... The merits of such a provisional rejection ***can*** be addressed by both the applicant and the Examiner without waiting for the first patent to issue.
>
> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications.
>
> ...
>
> ***If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection*** and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Here, the double patenting issue has not yet matured for rational argument (i.e., the copending application has not issued as a patent and the claims may be amended/cancelled in the future). Indeed, at a future time, the provisional double patenting rejection may be the only rejection remaining in the present application, in which case the rejection will be withdrawn in accordance with the provisions of MPEP 804.

Furthermore, Serial No. 11/113,861 is a continuation of Serial No. 09/581,772, which matured as O'Hagan above. Thus the arguments set forth above in connection with O'Hagan are to be considered for the present provisional double patenting rejection as well.

Claim Rejection under 35 USC §101

Withdrawal of the previous rejection under 35 USC §101 is noted with appreciation.

Rejection under 35 USC §112, 1st paragraph (enablement)--claims 40, 41 and 50

Withdrawal of the previous rejection of claims 40, 41 and 50 under 35 USC §112, 1st paragraph (enablement) is noted with appreciation.

Rejection under 35 USC §112, 1st paragraph (enablement)—claims 39, 42 and 44-48

Withdrawal of the previous rejection of claims 39, 42 and 44-48 under 35 USC §112, 1st paragraph (enablement) is noted with appreciation.

Rejection under 35 USC §112, 1st paragraph (enablement)—claim 38

Withdrawal of the previous rejection of claim 38 under 35 USC §112, 1st paragraph (enablement) is noted with appreciation.

Claim rejection under 35 USC §102(e)—O'Hagan

Various claims are rejected under 35 USC §102(e) as being anticipated by O'Hagan. This rejection is traversed.

As indicated in MPEP 2131, for a claim to be anticipated:

> ..."The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990)....

Thus, rejections under 35 U.S.C. § 102 are proper only when the claimed subject matter is *identically* described in the prior art.

Independent claim 1 presently requires, *inter alia*, microparticles comprising (a) a biodegradable polymer; (b) a cationic surfactant; and (c) an adsorbed polynucleotide-containing species constituting at least 5 percent of the total weight of the microparticles, wherein the cationic surfactant is present during formation of the microparticles, and wherein no cationic surfactant removal step is conducted subsequent to formation of the microparticles.

Dependent claim 27 further requires that the adsorbed polynucleotide-containing species constitute 10 to 30 percent of the total weight of the microparticles.

Dependent claims 28, 91 and 93 further require that the adsorbed polynucleotide-containing species constitute 10 to 20 percent of the total weight of the microparticles.

These loadings constitute elevated loading levels relative to those previously demonstrated. By increasing polynucleotide-containing species loading levels one can, *inter*

alia, reduce the amount of polymer that is administered to an animal (for a given dose of polynucleotide-containing species). See paragraph [0006] of the present specification.

The Office Action states that O'Hagan "defines" microparticles as having "a macromolecule to microparticle ratio in the range of 0.1 to 5%". Instead, O'Hagan teaches that "macromolecules are added to the microparticles to yield microparticles with adsorbed macromolecules having a weight to weight ratio of from about 0.0001:1 to 0.25:1 macromolecules to microparticles, preferably, 0.001:1 to 0.1, more preferably 0.01 to 0.05." See col. 14, lines 6-10.

Moreover, this passage pertains generally to "macromolecules," which are defined at col. 5, lines 65 *et seq.* to refer to "without limitation, a pharmaceutical, a polynucleotide, a polypeptide, a hormone, an enzyme, a transcription or translation mediator, an intermediate in a metabolic pathway, an immunomodulator, an antigen, an adjuvant, or combinations thereof."

Moreover, even assuming that all ranges of O'Hagan are applicable in their entirety to the entire range of species embraced by the term "macromolecules," the ranges described are not sufficiently specific to constitute an anticipation under the statute and the case law. In this regard, the standard for anticipation is high:

> When the prior art discloses a range which touches *>or< overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, >and< the reference teaches a broad range, ** depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. **>See, e.g., *Atofina v. Great Lakes Chem. Corp*, 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) wherein the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. Further, while there was a slight overlap between the reference's preferred range (150-350 degrees C) and the claimed range, that overlap was not sufficient for anticipation. "[T]he disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." *Id.* at 1000, 78 USPQ2d at 1424...

MPEP 2131.03. The facts of the present case are analogous to those above, if not more favorable to Applicant. As above, no specific examples falling within the claimed range are disclosed by O'Hagan. Moreover, with respect to the broad range disclosed by O'Hagan (i.e., microparticles with adsorbed macromolecules having a weight to weight ratio of from 0.0001:1 to 0.25:1), the

high "macromolecule" concentration is more than three orders of magnitude (2500 times) higher than the low macromolecule concentration (*cf.* the relatively narrow concentration ranges of claims 1, 27, 28, 52, 91 and 93). In this regard, please note that it was held by the Federal Circuit in *Atofina, supra*, that a much narrower disclosure of 100-500 degrees C by a prior art reference (i.e., a range of 5 times, or less than an order of magnitude) did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. This was true even though the claimed range was completely embraced by the range taught in the reference. With respect to the narrow range disclosed in O'Hagan (i.e., microparticles with adsorbed macromolecules having a weight to weight ratio of from 0.01 to 0.05), there is no overlap between the ranges of instant claims 27, 28, 52, 91 and 93, and only the lower endpoint of instant claim 1 appears to touch this range. See *Atofina* ("the disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points"). Moreover, it is worth emphasizing that whereas the prior art and claimed ranges in *Atofina* were based on an "apples-to-apples" comparison (i.e., degrees C vs. degrees C), in the present case the comparison is more of a "fruit-to-apples" comparison (i.e., macromolecule vs. polynucleotide-containing species).

Example 7 of O'Hagan describes pCMVgp120 DNA loads ranging from 0.84 to 2.36% with decreasing loading efficiencies ranging from 88% to 59%. The Office Action urges that "the loading efficiency is not 100% and therefore, in order to achieve a loading of 5%, one would have to use more than 5% input polynucleotide." However, this is not at all clear, as loading efficiency was seen to decrease with increasing target load.

In view of the above, it is respectfully submitted that claims 1, 27, 28, 52, 91 and 93, and those claims depending therefrom, are not anticipated by O'Hagan, at least in that the claimed amounts of adsorbed polynucleotide-containing species are not disclosed with "sufficient specificity" to constitute an anticipation of the claims.

With respect to cationic detergent, claim 52 sets forth a process in which a w/o/w emulsion is formed that comprises polymer and cationic surfactant, wherein the weight-to-weight surfactant-to-polymer ratio is in the range of from 0.0025:1 to about 0.05:1.

O'Hagan teaches that "a weight to weight detergent to polymer ratio in the range of from about 0.00001:1 to about 0.1:1 will be used, more preferably from about 0.0001:1 to about 0.01:1, more preferably from about 0.001:1 to about 0.01:1, and even more preferably from

about 0.005:1 to about 0.01:1." See col. 13, lines 32-37. This passage, however, pertains generally to "detergents," which are defined at col. 5, lines 28-36 to "include surfactants and emulsion stabilizers. Anionic detergents include, but are not limited to, SDS, SLS, sulphated fatty alcohols, and the like. Cationic detergents include, but are not limited to, cetrimide (CTAB), benzalkonium chloride, DDA (dimethyl dioctodecyl ammonium bromide), DOTAP, and the like. Nonionic detergents include, but are not limited to, sorbitan esters, polysorbates, polyoxyethylated glycol monoethers, polyoxyethylated alkyl phenols, poloxamers, and the like."

Moreover, to the extent that these ranges embrace the ranges of method claim 52, they are not sufficiently specific to constitute anticipation under the statute and the case law. See *Atofina supra*. As above, it is worth emphasizing that whereas the prior art and claimed ranges in *Atofina* were based on an "apples-to-apples" comparison (i.e., degrees C vs. degrees C), in the present case the comparison is more of a "fruit-to-apples" comparison (i.e., detergents vs. cationic detergent).

Turning to Example 2 of O'Hagan, 12.5 ml of a 4% PLG solution (which contains 0.5 g PLG) and a 50 ml of a 0.5% CTAB solution (which contains 0.25 g CTAB) are employed, corresponding to 50% CTAB relative to PLG, or a weight-to-weight surfactant-to-polymer ratio of 0.5:1. This is the same percentage as described in Singh *infra*. These percentages are much greater that the range of cationic surfactant used in claim 52. See also Example 1 of the present specification, wherein 16.6 ml of a 6 % PLG solution (which contains 1 g PLG) and a solution containing 10 mg CTAB are employed, corresponding to 1% CTAB relative to PLG. A repeat procedure employed 4% CTAB relative to PLG.

Note also that the 50% CTAB relative to PLG used in producing the microparticles of O'Hagan is *outside* even the broadest weight to weight detergent to polymer ratio range described in O'Hagan (i.e., a range of from about 0.00001:1 to about 0.1:1). However, the microparticles produced by O'Hagan using 50% CTAB relative to PLG are washed with water by centrifugation four times. As indicated in Singh *infra* (page 815, right column, third paragraph), washing twice with water by centrifugation results in a CTAB level of 4 micrograms of CTAB per milligram of PLG polymer, or a CTAB concentration of 0.4% relative to PLG. The amount of CTAB in the microparticles of Example 2 of O'Hagan, which were washed four times (rather than two) would be expected to be at least as low, given that the same relative amount of CTAB was used to form the microparticles of O'Hagan as was used in Singh.

Unlike O'Hagan (and Singh), the microparticles in claims 1 and 52 are not washed to remove cationic surfactant subsequent to microparticle formation. This is also true of the microparticles of Examples 1 and 2 in the present specification--consequently, the same amount of detergent used to form the microparticles (1% and 4% CTAB relative to PLG) is also present in the microparticles to which the DNA was adsorbed. In O'Hagan, even though 50% CTAB relative to PLG was used in producing the microparticles, the amount of detergent in the microparticles to which the DNA is adsorbed is far less (not more than 0.4% CTAB relative to PLG, for the reasons discussed above). This amount is also less than the amount of cationic detergent in claims 97, 100 and 101.

Note that it is not at all obvious to eliminate a cationic surfactant removal step as claimed (e.g., by a method such as centrifugation with washing). As indicated in Singh *infra* (page 815, right column, third paragraph) there is strong incentive to keep the CTAB levels to a minimum.

Finally, as seen from Tables 3 and 4 of the present specification, microparticles with levels of cationic detergent like those claimed in claims 97, 100 and 101 were unexpectedly found to exhibit enhanced immunogenicity, not only relative to naked DNA, but also relative to microparticles having higher amounts of cationic detergent. This is surprising, given the higher loading efficiencies, and thus higher loadings, observed with higher amounts of cationic detergent.

For at least these reasons, reconsideration and withdrawal of claim rejection under 35 USC §102(e) are requested.

Claim rejection under 35 USC §103(a)—Singh

Various claims are rejected under 35 USC §103(a) as being unpatentable over Singh et al., *Proc. Natl. Acad. Sci. USA*, 2000, 97:811-816 (Singh). This rejection is traversed.

The deficiencies in Singh are similar to those of O'Hagan.

For example, see Table 1 of Singh, in which loading levels of 0.92%, 0.68% and 0.62% are described. The Examiner argues that although the claimed ranges are not disclosed, it is obvious and routine in the art to vary certain parameters, including loading, composition and ratio between different components.. As evidence, the Examiner points to Table 2 and Fig. 2 of Singh. However, these data represent evidence of optimization of gene expression with respect

to *dose*, rather than optimization of gene expression with respect to microparticle *loading*, which is a different concept.

With respect to dose, Singh reports only a single procedure for forming PLG/CTAB Luc DNA microparticles (i.e., those formed by incubating 100 mg cationic microparticles in a 1 mg/ml solution of DNA--see page 812) for use therein. With only a single type of microparticle reported (i.e., those formed by the foregoing procedure), one of ordinary skill in the art would understand that in order to increase total DNA dose by a factor of 10 (see Fig. 2) the amount of the microparticle composition administered would be increased by a factor of 10, and vice versa.

With respect to loading, as noted in MPEP 2144.05, a particular parameter must first be recognized as a result-effective variable before it can be argued that it is obvious to optimize the parameter.

Finally, it is noted that the loading levels claimed are more than 5 times those described in Singh. See Table 1 of Singh, in which loading levels of 0.92%, 0.68% and 0.62% are described. Given that loading efficiency decreases with increased target loads (see O'Hagan above) , it is by no means obvious that the loading levels claimed are even achievable using the technology described in Singh.

As with O'Hagan above, it is further noted that in forming the CTAB microparticles of Singh, 0.5 g PLG (10 ml x 5% wt/vol) is combined with 0.25 g CTAB (50 ml x 0.5% wt/vol), which corresponds to 50% CTAB relative to PLG. Furthermore, the microparticles produced by Singh are washed with water by centrifugation. Unlike Singh, the microparticles in claims 1 and 52 are not washed to remove cationic surfactant subsequent to microparticle formation.

Moreover, as indicated in Singh (page 815, right column, third paragraph), washing twice with water by centrifugation results in a CTAB level of 4 micrograms of CTAB per milligram of PLG polymer, or a CTAB concentration of 0.4% relative to PLG. In the invention presently claimed in claims 97, 100 and 101, on the other hand, the microparticles comprise 0.5 to 2 wt% cationic surfactant. As with loading, there is no evidence that CTAB concentration is a result-effective variable.

Moreover, as seen from Tables 3 and 4 of the present specification, microparticles with lower amounts of cationic detergent (i.e., with amounts of cationic detergent like those claimed in claims 97, 100 and 101) were unexpectedly found to exhibit enhanced immunogenicity, not only relative to naked DNA, but also relative to microparticles having higher amounts of cationic

detergent. This is surprising, given the higher loading efficiencies observed with higher amounts of cationic detergent.

For at least the above reasons, reconsideration and withdrawal of the claim rejection under 35 USC §103(a) over Singh are requested.

Claim rejection under 35 USC §103(a)—Singh, Thalhamer, Diwan

Various claims are rejected under 35 USC §103(a) as being unpatentable over Singh and further in view of Thalhamer et al., *Endocrine Regulations*, 2001, 35:143-166 (Thalhamer) as evidenced by Diwan et al., *Journal of Controlled Release*, 2002, 85:247-262 (Diwan). This rejection is traversed.

Various deficiencies in Singh as a reference are noted above. Thalhamer and Diwan, which are cited for their teachings regarding CpG adjuvants, do not make up for those deficiencies in Singh.

Moreover, while Thalhamer and Diwan may teach CpG adjuvants, they do not teach adsorbing them to microparticles as claimed in certain claims (see, e.g., claim 8). The Examiner recognizes this, but argues that both references teach CpG in combination with DNA vaccines and that Devan teaches that the co-delivery of CpG and antigen *in nanoparticles* is more efficient than the delivery of antigen in nanoparticles and CpG in solution. Be that as it may, it continues to be the case that Thalhamer and Diwan do not teach or suggest the adsorption of CpG oligonucleotides to microparticles, or even adsorption to nanoparticles for that matter.

For at least the above reasons, reconsideration and withdrawal of the claim rejection under 35 USC §103(a) based on Singh, Thalhamer and Diwan are requested.

CONCLUSION

Applicant submits that this application is in condition for allowance, early notification of which is earnestly solicited. The Examiner is encouraged to contact the undersigned at (703) 433-0510 to discuss any outstanding issues in this case.

FEES

The Office is authorized to charge the two-month extension fee ($450) and any additional fees that are due as a result of this Response, and to credit any overpayments, to the undersigned attorney's PTO Deposit Account #50-1047.

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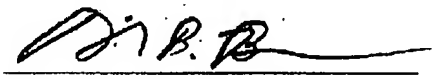
Respectfully submitted,



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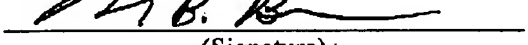

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